

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE  
in its capacity as elected Office

Date of mailing (day/month/year) 19 January 2001 (19.01.01)	
International application No. PCT/US00/10555	Applicant's or agent's file reference AHP28APCT
International filing date (day/month/year) 19 April 2000 (19.04.00)	Priority date (day/month/year) 21 April 1999 (21.04.99)
Applicant PACHUK, Catherine et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
03 November 2000 (03.11.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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# INTERNATIONAL COOPERATION TREATY

## PCT

From the INTERNATIONAL SEARCHING AUTHORITY

### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:  
Howson and Howson  
Attn. BAK Mary E.  
Spring House Corporate Cntr.,  
P.O. Box 457  
Spring House, PA 19477  
UNITED STATES OF AMERICA

NOV 20 2000

Date of mailing  
(day/month/year) 15/11/2000

Applicant's or agent's file reference

AHP28APCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US 00/10555

International filing date  
(day/month/year)

19/04/2000

Applicant

AMERICAN HOME PRODUCTS CORPORATION et al.

ENTERED  
DUE 15-01

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

#### Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-2016

Authorized officer

Chantal Meyer

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>AHP28APCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 10555</b>	International filing date (day/month/year) <b>19/04/2000</b>	(Earliest) Priority Date (day/month/year) <b>21/04/1999</b>
Applicant  <b>AMERICAN HOME PRODUCTS CORPORATION et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of Invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PC 00/10555

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/11 C12N15/63 C12N15/70 C12N15/86 C07K14/01  
C07K14/08 A61K48/00 A61K38/16 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MONTGOMERY M K ET AL: "Double-stranded RNA as a mediator in sequence-specific genetic silencing and co-suppression" TRENDS IN GENETICS, NL, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 14, no. 7, 1 July 1998 (1998-07-01), pages 255-258, XP004124680 ISSN: 0168-9525 the whole document ---	1
X	WO 95 27783 A (JOSHI SUKHWAL SADNA) 19 October 1995 (1995-10-19)  page 8, line 29 -page 11, line 10 --- -/--	1, 4, 5, 8, 9, 28, 32-40, 42-45, 48, 55, 56, 58, 61-63



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

30 October 2000

Date of mailing of the international search report

15/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Mateo Rosell, A.M.

## INTERNATIONAL SEARCH REPORT

International Application No

P00000/10555

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 05770 A (ROTHBARTH KARSTEN ; JOSWIG GABY (DE); WERNER DIETER (DE); SCHUBERT) 12 February 1998 (1998-02-12) cited in the application  the whole document ---	1,6,8, 18,20, 23-25, 28,30, 31, 33-40, 49,59, 60,64
X	WO 97 34638 A (UNIV CALIFORNIA) 25 September 1997 (1997-09-25)  page 3, line 5 -page 4, line 28; examples 1,2 ---	1,6,8, 13,28, 32-34, 42-45, 48,55-67
X	PLAYER MARK R ET AL: "Targeting HIV mRNA for degradation: 2,5-A antisense chimeras as potential chemotherapeutic agents for AIDS." NUCLEOSIDES & NUCLEOTIDES, vol. 16, no. 7-9, July 1997 (1997-07), pages 1221-1222, XP000952972 ISSN: 0732-8311 the whole document ---	1,42-45
A	WO 97 07825 A (UNIV COLORADO) 6 March 1997 (1997-03-06)  page 3, line 5 -page 5, line 20 page 8, line 3-23 ---	1,6,8, 10,17, 28,33, 34,45
A	US 4 891 315 A (WEIS JOHN H ET AL) 2 January 1990 (1990-01-02) the whole document ---	1,42,45
A	MIKITA T ET AL: "EFFECTS OF ARABINOSYLCYTOSINE-SUBSTITUTED DNA ON DNA/RNA HYBRID STABILITY AND TRANSCRIPTION BY T7 RNA POLYMERASE" BIOCHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, PA, vol. 33, 1994, pages 9195-9208, XP000882431 ISSN: 0006-2960 the whole document ---	1

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## INTERNATIONAL SEARCH REPORT

International Application No

PC 93 00/10555

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YUKIKO TONE ET AL: "STRUCTURE AND CHROMOSOMAL LOCATION OF THE MOUSE INTERLEUKIN-12 P35 AND P40 SUBUNIT GENES" EUROPEAN JOURNAL OF IMMUNOLOGY, DE, WEINHEIM, vol. 26, no. 6, 1 June 1996 (1996-06-01), pages 1222-1227, XP000612644 ISSN: 0014-2980 cited in the application the whole document ---	1
A	JAEGER J A ET AL: "IMPROVED PREDICTIONS OF SECONDARY STRUCTURES FOR RNA" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 86, no. 20, 1989, pages 7706-7710, XP000953154 1989 ISSN: 0027-8424 cited in the application the whole document ---	2
A	WATERHOUSE ET AL: "Virus resistance and gene silencing in plants can be induced by simultaneous expression of sense and antisense RNA" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 95, November 1998 (1998-11), pages 13959-13964, XP002114472 ISSN: 0027-8424 the whole document ---	1, 42
A	NELLEN W ET AL: "WHAT MAKES AN MRNA ANTI-SENSE-ITIVE?" TIBS TRENDS IN BIOCHEMICAL SCIENCES, EN, ELSEVIER PUBLICATION, CAMBRIDGE, vol. 18, no. 11, 1 November 1993 (1993-11-01), pages 419-423, XP002049385 ISSN: 0968-0004 the whole document ---	1
A	FIRE A ET AL: "Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans" NATURE, GB, MACMILLAN JOURNALS LTD. LONDON, vol. 391, 19 February 1998 (1998-02-19), pages 806-811, XP002095876 ISSN: 0028-0836 the whole document ---	1

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## INTERNATIONAL SEARCH REPORT

International Application No

P000000000000/10555

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>WIANNY F ET AL: "Specific interference with gene function by double-stranded RNA in early mouse development" NATURE CELL BIOLOGY, GB, MACMILLAN PUBLISHERS, vol. 2, no. 2, February 2000 (2000-02), pages 70-75, XP002138445 ISSN: 1465-7392 the whole document</p> <p>---</p>	1,3,6,8, 9
P,X	<p>WO 99 53050 A (WANG MING BO ; COMMW SCIENT IND RES ORG (AU); GRAHAM MICHAEL WAYNE) 21 October 1999 (1999-10-21) cited in the application</p> <p>page 1, line 1-17 page 8, line 5 -page 10, line 20 page 22, line 4 -page 23, line 2 page 26, line 1-25</p> <p>---</p>	1,3-6,8, 10-16, 35-40, 42, 61-63,65
E	<p>WO 00 44914 A (FARRELL MICHAEL J ; LI YIN XIONG (US); KIRBY MARGARET L (US); MEDIC) 3 August 2000 (2000-08-03) page 2, line 20 -page 5, line 10 page 10, line 4 -page 19, line 17; example III</p> <p>---</p>	1,3,6,8, 9,28,33, 34,42
T	<p>CAPLEN N J ET AL: "dsRNA-mediated gene silencing in cultured Drosophila cells: a tissue culture model for the analysis of RNA interference" GENE, ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, NL, vol. 252, no. 1-2, 11 July 2000 (2000-07-11), pages 95-105, XP004210158 ISSN: 0378-1119 abstract page 96, left-hand column, paragraph 2 page 102, left-hand column, last paragraph -page 104, left-hand column, last paragraph</p> <p>---</p>	1,9,28, 31,33,34
T	<p>PARK WEE-SUNG ET AL: "Inhibition of HIV-1 replication by a new type of circular dumbbell RNA/DNA chimeric oligonucleotides." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 270, no. 3, 21 April 2000 (2000-04-21), pages 953-960, XP002151277 ISSN: 0006-291X the whole document</p> <p>-----</p>	1,6,8, 42-45, 55,56, 58, 61-63,65

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,42,46,48,49,52-63

Present claims 1,42,46,48,49 and 52-63 relate to an extremely large number of possible compounds (agents and/or target polynucleotides). In fact, the claims contain so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely, (a) agents: partially ds-RNA, dsRNA, ss-RNA sense and antisense, circular RNA, lariats and hybrid RNA-DNA as mentioned in the description at pages 8, line 5 to page 9, line 4, and page 14, line 1 to page 16, line 22, and (b) target polynucleotides gag gene of HIV, the gD gene of HSV, type 2 genome and to a polynucleotide sequence homologous to IL-12p40 murine messenger RNA as recited in examples 1-4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 00/10555

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 55-60 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1,42,46,48,49,52-63  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 00/10555

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9527783 A	19-10-1995	AU 2133695 A	30-10-1995
W0 9805770 A	12-02-1998	DE 19631919 A EP 0918853 A	12-02-1998 02-06-1999
W0 9734638 A	25-09-1997	AU 2585197 A	10-10-1997
W0 9707825 A	06-03-1997	US 5766903 A AU 7103796 A CA 2229454 A EP 0846002 A	16-06-1998 19-03-1997 06-03-1997 10-06-1998
US 4891315 A	02-01-1990	AT 59679 T CA 1295561 A DE 3382072 D DK 333183 A EP 0101655 A ES 524245 D ES 8504254 A ES 529225 D ES 8505253 A FI 832632 A, B, GR 78647 A IE 56902 B IL 69269 A NO 832626 A, B, NZ 204948 A PH 21239 A PL 243134 A PT 77014 A, B US 4673641 A AU 1678783 A JP 2786625 B JP 59118097 A JP 2780961 B JP 8266289 A JP 8294392 A	15-01-1991 11-02-1992 07-02-1991 21-01-1984 29-02-1984 01-04-1985 01-07-1985 16-05-1985 01-09-1985 21-01-1984 27-09-1984 29-01-1992 15-12-1989 23-01-1984 30-10-1987 21-08-1987 13-08-1984 01-08-1983 16-06-1987 26-01-1984 13-08-1998 07-07-1984 30-07-1998 15-10-1996 12-11-1996
W0 9953050 A	21-10-1999	AU 2951499 A	01-11-1999
W0 0044914 A	03-08-2000	NONE	

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

## INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

### What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

### What documents must/may accompany the amendments?

#### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

**"Statement under article 19(1)" (Rule 46.4)**

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

**Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

**Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

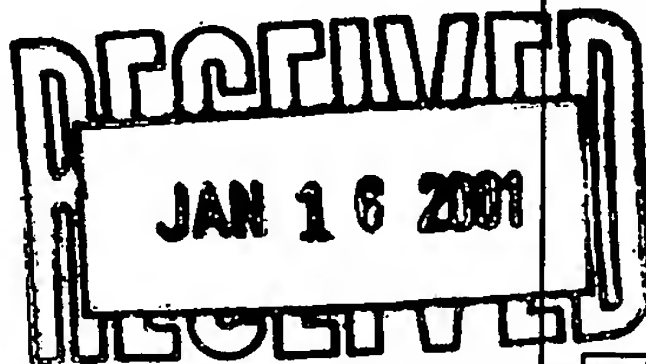
For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

# PATENT COOPERATION TREATY

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BAK Mary E.  
Howson and Howson  
Spring House Corporate Cntr.,  
P.O. Box 457  
Spring House, PA 19477  
ETATS-UNIS D'AMERIQUE



## PCT

### WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference <b>AHP28APCT</b>		Date of mailing (day/month/year) <b>09.01.2001</b>
International application No. <b>PCT/US00/10555</b>		International filing date (day/month/year) <b>19/04/2000</b>
International Patent Classification (IPC) or both national classification and IPC <b>C12N15/11</b>		Priority date (day/month/year) <b>21/04/1999</b>
Applicant <b>AMERICAN HOME PRODUCTS CORPORATION et al.</b>		

**ENTERED  
DUE 4-1-01**

- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
  - ☒ Basis of the opinion
  - ☐ Priority
  - ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - ☐ Lack of unity of invention
  - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - ☒ Certain document cited
  - ☒ Certain defects in the international application
  - ☒ Certain observations on the international application
- The applicant is hereby invited to reply to this opinion.
 

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 21/08/2001.

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich

Authorized officer / Examiner

**SCHEFFZYK, I**

Formalities officer (incl. extension of time limits)



**SECTION V-----**

Remark: Applicant's attention is drawn to the fact that this written opinion only relates to subject-matter which had been searched (see form PCT/ISA/210 issued on 15/11/00).

The disclosures of WO95/27783 (1), WO 97/34638 (2) and WO 98/05770 (3) are deemed novelty destroying for the subject-matter of claims 1, 2, 4-15, 18-25, 28, 30, 32-34, 42-45, 48, 52, 55, 56, 58, 60-63 (see e.g. (1) concerning claims 1, 2, 4-10, 28, 30, 32-34, 42-45, 48, 52, 55, 56, 58, 60-63 and (2) concerning claims 1, 2, 4, -15, 18-25, 28, 30, 33, 34, 52 and (3) concerning claims 1, 2, 4, 5, 6, 7, 9, 28, 32-34, 42-45, 48 and 52). With respect to claims 2, 4 and 5 it is noted that although none of the cited documents expressly mentions the features given in said claims at present novelty of these claims cannot be acknowledged since it cannot be ruled out that the RNAs taught in (1), (2) or (3) inherently exhibit these features. The same applies correspondingly to claims 11, 12, 14, 15, 21, 22, 24 and 25. Concerning claims 6-8 it is noted that these claims do not contain any technical features which would be suitable to render the claimed composition novel over those taught in (1)-(3).

Thus, claims 1, 2, 4-15, 18-25, 28, 30, 32-34, 42-45, 48, 52, 55, 56, 58, 60-63 do not comply with the requirements of Art. 33(2)(3) PCT.

The principle underlying present application, i.e. the use of (antisense) ds RNA as agent to treat viral infections, such as for instance Aids, or cancer is already taught in the prior art (see e.g. (1), (3), Montgomery M.K. et al., Trends in Genetics vol. 14, no. 7, 01.07.98, pp. 255-258 (4) and Player M. et al., Nucleosides and Nucleotides, vol. 16, no. 7-9, 07/97 (5)). Correspondingly, in view of the teachings of these prior art documents the subject-matter of present claims cannot be considered to be inventive. Thus, claims 1-67 do not meet the requirements of Art.33(2)(3) PCT.

**SECTION VI-----**

WO 99/53050



WO 00/44914

Wianny F. et al, Nature Cell Biology, vol. 2, no. 2, February 2000, pp. 70-75

**SECTION VII-----**

- 1). With respect to the expression "incorporated by reference" Applicant's attention is drawn to Guidelines C-II 4.4 and 4.17 PCT.
- 2). The Serial numbers mentioned in the specification should be replaced by the corresponding publication numbers.

**SECTION VIII-----**

- 1). The terms "essential" and "substantially" are relative terms and thus open to interpretation. Correspondingly, the use thereof render the scope of claims unclear (Art. 6 PCT).
- 2). In addition, in the absence of an indication concerning the percental identity between sequences the term "homologous" also is open to interpretation. Thus the use of said term also renders the scope of claims unclear.
- 3). Claim 2 is unclear: on the one hand said claim requires that at least 11 contiguous nucleotides are present in a double-stranded form but on the other hand it gives preconditions (depending...)?
- 4). Claim 51 is unclear since a fusion does not necessarily contain a "spanning sequence"
- 5). Claims 57, 59, 60, and 64 lack technical support by the specification.
- 6). Claims 55-60 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these

**WRITTEN OPINION  
SEPARATE SHEET**

---

International application No. PCT/US00/10555

claims (Article 34(4)(a)(i) PCT).

**I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-44 as originally filed

**Claims, No.:**

1-67 as originally filed

**Drawings, sheets:**

1/1 as originally filed

**Sequence listing part of the description, pages:**

1-6, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☐ claims Nos. ,

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1, 42, 46, 48, 49, 52-63 partial (see PCT/ISA210 issued on 15.11.00).

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Claims	1,2,4-15,18-25,28,30,32-34,42-45,48,52,55,56,58,60-63
Inventive step (IS)	Claims	1-67
Industrial applicability (IA)	Claims	55-60: see section VIII/5).

**2. Citations and explanations  
see separate sheet****VI. Certain documents cited****1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)****see separate sheet****VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**se separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**se separate sheet**



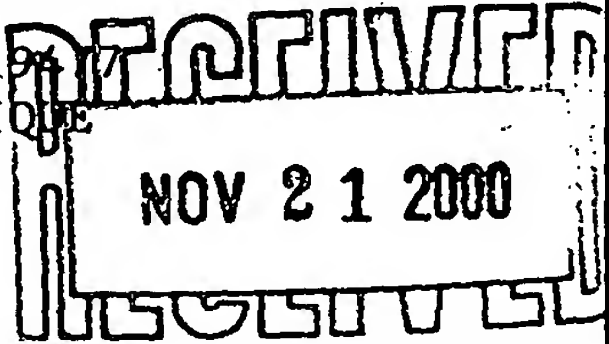
# PATENT COOPERATION TREATY

# PCT

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BAK Mary E.  
Howson and Howson  
Spring House Corporate Cntr.,  
P.O. Box 457  
Spring House, PA 19417  
ETATS-UNIS D'AMERIQUE



## NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence  
and Administrative Instructions, Section 601(a))

Date of mailing  
(day/month/year)

16. 11. 00

Applicant's or agent's file reference  
AHP28APCT

### IMPORTANT NOTIFICATION

International application No.

PCT/US 00/ 10555

International filing date (day/month/year)

19/04/2000

Priority date (day/month/year)

21/04/1999

Applicant

AMERICAN HOME PRODUCTS CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

03/11/2000

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).  
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).  
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel (+49-89) 2399-0, Tx: 523656 epmu d

Authorized officer

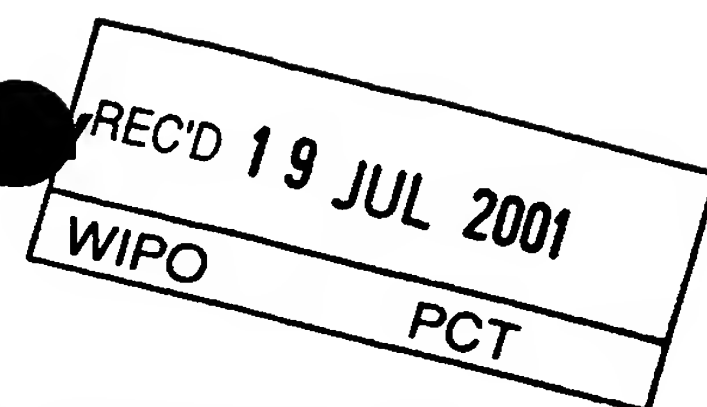
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PATENT COOPERATION TREATY

PCT



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference <b>AHP28APCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/US00/10555</b>	International filing date (day/month/year) <b>19/04/2000</b>	Priority date (day/month/year) <b>21/04/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>C12N15/11</b>		
Applicant <b>AMERICAN HOME PRODUCTS CORPORATION et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
  - I ☒ Basis of the report
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☒ Certain documents cited
  - VII ☒ Certain defects in the international application
  - VIII ☒ Certain observations on the international application

Date of submission of the demand  <b>03/11/2000</b>	Date of completion of this report  <b>17.07.2001</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>SCHEFFZYK, I</b>  Telephone No. +49 89 2399 8602  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/10555

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*):

### Description, pages:

1-44 as originally filed

### Claims, No.:

1-67 as originally filed

### Drawings, sheets:

1/1 as originally filed

### Sequence listing part of the description, pages:

1-6, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/10555

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☐ claims Nos. .

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1, 42, 46, 48, 49, 52-63 partial (see PCT/ISA210 issued on 15.11.00).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

### V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/10555

## **citati ns and xplanati ns supporting such stat ment**

### **1. Statement**

Novelty (N)	Yes:	Claims	3,16,17,26,27,29,31,35-41,46,47,49-51,53,54,57,59,64-67
	No:	Claims	1,2,4-15,18-25,28,30,32-34,42-45,48,52,55,56,58,60-63
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-67
Industrial applicability (IA)	Yes:	Claims	1-54,61-67
	No:	Claims	55-60: see section VIII/5).

### **2. Citations and explanations see separate sheet**

## **VI. Certain documents cited**

### **1. Certain published documents (Rule 70.10)**

and / or

### **2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

## **VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

## **VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**se separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/US00/10555

**SECTION V-----**

Remark: Applicant's attention is drawn to the fact that this IPER only relates to subject-matter which had been searched (see form PCT/ISA/210 issued on 15/11/00).

The disclosures of WO95/27783 (1), WO 97/34638 (2) and WO 98/05770 (3) are deemed novelty destroying for the subject-matter of claims 1, 2, 4-15, 18-25, 28, 30, 32-34, 42-45, 48, 52, 55, 56, 58, 60-63 (see e.g. (1) concerning claims 1, 2, 4-10, 28, 30, 32-34, 42-45, 48, 52, 55, 56, 58, 60-63 and (2) concerning claims 1, 2, 4, -15, 18-25, 28, 30, 33, 34, 52 and (3) concerning claims 1, 2, 4, 5, 6, 7, 9, 28, 32-34, 42-45, 48 and 52). With respect to claims 2, 4 and 5 it is noted that although none of the cited documents expressly mentions the features given in said claims at present novelty of these claims cannot be acknowledged since it cannot be ruled out that the RNAs taught in (1), (2) or (3) inherently exhibit these features. The same applies correspondingly to claims 11, 12, 14, 15, 21, 22, 24 and 25. Concerning claims 6-8 it is noted that these claims do not contain any technical features which would be suitable to render the claimed composition novel over those taught in (1)-(3).

Thus, claims 1, 2, 4-15, 18-25, 28, 30, 32-34, 42-45, 48, 52, 55, 56, 58, 60-63 do not comply with the requirements of Art. 33(2)(3) PCT.

The principle underlying present application, i.e. the use of (antisense) ds RNA as agent to treat viral infections, such as for instance Aids, or cancer is already taught in the prior art (see e.g. (1), (3), Montgomery M.K. et al., Trends in Genetics vol. 14, no. 7, 01.07.98, pp. 255-258 (4) and Player M. et al., Nucleosides and Nucleotides, vol. 16, no. 7-9, 07/97 (5)). Correspondingly, in view of the teachings of these prior art documents the subject-matter of present claims cannot be considered to be inventive. Thus, claims 1-67 do not meet the requirements of Art.33(2)(3) PCT.

**SECTION VI-----**

WO 99/53050

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US00/10555

WO 00/44914

Wianny F. et al, Nature Cell Biology, vol. 2, no. 2, February 2000, pp. 70-75

**SECTION VII-----**

- 1). With respect to the expression "incorporated by reference" Applicant's attention is drawn to Guidelines C-II 4.4 and 4.17 PCT.
- 2). The Serial numbers mentioned in the specification should be replaced by the corresponding publication numbers.

**SECTION VIII-----**

- 1). The terms "essential" and "substantially" are relative terms and thus open to interpretation. Correspondingly, the use thereof render the scope of claims unclear (Art. 6 PCT).
- 2). In addition, in the absence of an indication concerning the percental identity between sequences the term "homologous" also is open to interpretation. Thus the use of said term also renders the scope of claims unclear.
- 3). Claim 2 is unclear: on the one hand said claim requires that at least 11 contiguous nucleotides are present in a double-stranded form but on the other hand it gives preconditions (depending...)?
- 4). Claim 51 is unclear since a fusion does not necessarily contain a "spanning sequence"
- 5). Claims 57, 59, 60, and 64 lack technical support by the specification.
- 6). Claims 55-60 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/US00/10555

claims (Article 34(4)(a)(i) PCT).



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C12N 15/11, 15/63, 15/70, 15/86, C07K 14/01, 14/08, A61K 48/00, 38/16, A61P 35/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 00/63364</b> <b>(43) International Publication Date:</b> 26 October 2000 (26.10.00)
<b>(21) International Application Number:</b> PCT/US00/10555 <b>(22) International Filing Date:</b> 19 April 2000 (19.04.00) <b>(30) Priority Data:</b> 60/130,377 21 April 1999 (21.04.99) US <b>(71) Applicant (for all designated States except US):</b> AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> PACHUK, Catherine [US/US]; 3212 New Park Circle, Lansdale, PA 19446 (US). SATISHCHANDRAN, C. [US/US]; 605 Shepard Drive, Lansdale, PA 19446 (US). <b>(74) Agents:</b> BAK, Mary, E. et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).		<b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> METHODS AND COMPOSITIONS FOR INHIBITING THE FUNCTION OF POLYNUCLEOTIDE SEQUENCES <b>(57) Abstract</b> <p>A therapeutic composition for inhibiting the function of a target polynucleotide sequence in a mammalian cell includes an agent that provides to a mammalian cell an at least partially double-stranded RNA molecule comprising a polynucleotide sequence of at least about 200 nucleotides in length, said polynucleotide sequence being substantially homologous to a target polynucleotide sequence. This RNA molecule desirably does not produce a functional protein. The agents useful in the composition can be RNA molecules made by enzymatic synthetic methods or chemical synthetic methods <i>in vitro</i>; or made in recombinant cultures of microorganisms and isolated therefrom, or alternatively, can be capable of generating the desired RNA molecule <i>in vivo</i> after delivery to the mammalian cell. In methods of treatment of prophylaxis of virus infections, other pathogenic infections or certain cancers, these compositions are administered in amounts effective to reduce or inhibit the function of the target polynucleotide sequence, which can be of pathogenic origin or produced in response to a tumor or other cancer, among other sources.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TC	Togo
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CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,42,46,48,49,52-63

Present claims 1,42,46,48,49 and 52-63 relate to an extremely large number of possible compounds (agents and/or target polynucleotides). In fact, the claims contain so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely, (a) agents: partially ds-RNA, dsRNA, ss-RNA sense and antisense, circular RNA, lariats and hybrid RNA-DNA as mentioned in the description at pages 8, line 5 to page 9, line 4, and page 14, line 1 to page 16, line 22, and (b) target polynucleotides gag gene of HIV, the gD gene of HSV, type 2 genome and to a polynucleotide sequence homologous to IL-12p40 murine messenger RNA as recited in examples 1-4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/10555

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/11 C12N15/63 C12N15/70 C12N15/86 C07K14/01  
C07K14/08 A61K48/00 A61K38/16 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MONTGOMERY M K ET AL: "Double-stranded RNA as a mediator in sequence-specific genetic silencing and co-suppression" TRENDS IN GENETICS, NL, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 14, no. 7, 1 July 1998 (1998-07-01), pages 255-258, XP004124680 ISSN: 0168-9525 the whole document	1
X	WO 95 27783 A (JOSHI SUKHWAL SADNA) 19 October 1995 (1995-10-19)  page 8, line 29 -page 11, line 10 --- -/--	1, 4, 5, 8, 9, 28, 32-40, 42-45, 48, 55, 56, 58, 61-63

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## ° Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 "&" document member of the same patent family

Date of the actual completion of the international search

30 October 2000

Date of mailing of the international search report

15/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Mateo Rosell, A.M.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/10555

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	PLAYER MARK R ET AL: "Targeting HIV mRNA for degradation: 2,5-A antisense chimeras as potential chemotherapeutic agents for AIDS." NUCLEOSIDES & NUCLEOTIDES, vol. 16, no. 7-9, July 1997 (1997-07), pages 1221-1222, XP000952972 ISSN: 0732-8311 the whole document ---	1,42-45
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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/10555

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YUKIKO TONE ET AL: "STRUCTURE AND CHROMOSOMAL LOCATION OF THE MOUSE INTERLEUKIN-12 P35 AND P40 SUBUNIT GENES" EUROPEAN JOURNAL OF IMMUNOLOGY, DE, WEINHEIM, vol. 26, no. 6, 1 June 1996 (1996-06-01), pages 1222-1227, XP000612644 ISSN: 0014-2980 cited in the application the whole document	1
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International Application No

PCT/US 00/10555

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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P, X	<p>WO 99 53050 A (WANG MING BO ; COMMW SCIENT IND RES ORG (AU); GRAHAM MICHAEL WAYNE) 21 October 1999 (1999-10-21) cited in the application</p> <p>page 1, line 1-17 page 8, line 5 -page 10, line 20 page 22, line 4 -page 23, line 2 page 26, line 1-25</p> <p>---</p>	1, 3-6, 8, 10-16, 35-40, 42, 61-63, 65
E	<p>WO 00 44914 A (FARRELL MICHAEL J ; LI YIN XIONG (US); KIRBY MARGARET L (US); MEDIC) 3 August 2000 (2000-08-03) page 2, line 20 -page 5, line 10 page 10, line 4 -page 19, line 17; example III</p> <p>---</p>	1, 3, 6, 8, 9, 28, 33, 34, 42
T	<p>CAPLEN N J ET AL: "dsRNA-mediated gene silencing in cultured Drosophila cells: a tissue culture model for the analysis of RNA interference" GENE, ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, NL, vol. 252, no. 1-2, 11 July 2000 (2000-07-11), pages 95-105, XP004210158 ISSN: 0378-1119 abstract page 96, left-hand column, paragraph 2 page 102, left-hand column, last paragraph -page 104, left-hand column, last paragraph</p> <p>---</p>	1, 9, 28, 31, 33, 34
T	<p>PARK WEE-SUNG ET AL: "Inhibition of HIV-1 replication by a new type of circular dumbbell RNA/DNA chimeric oligonucleotides." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 270, no. 3, 21 April 2000 (2000-04-21), pages 953-960, XP002151277 ISSN: 0006-291X the whole document</p> <p>-----</p>	1, 6, 8, 42-45, 55, 56, 58, 61-63, 65

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International Application No

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